REMARKS

Claims 23-39 were pending in the present application. Claims 23-34, 38 and 39 were withdrawn from consideration. By virtue of this response, claims 35 and 36 have been amended. Accordingly, claims 35-37 are currently under consideration. Amendment and cancellation of certain claims is not to be construed as a dedication to the public of any of the subject matter of the claims as previously presented. No new matter has been added.

Concerning the Information Disclosure Statement dated December 31, 2002

Applicants have enclosed legible copies of the references cited in the above referenced Information Disclosure Statement. Please note that Ref. No. 4, "Cloning and Chromosomal Localization of a Human Endothelin ETA Receptor" by Cyr, C. et al, has a sequence listing on page 186 that may be somewhat difficult to read in the original. We have attached to the back of that article, an enlarged copy of that page.

Concerning the Specification

The Office has objected to the specification due to informalities. In response, Applicants have provided substitute paragraphs for those paragraphs noted by the Examiner to include handwritten symbols.

Concerning the Claims

Claims 35 and 36 have been amended to no longer refer to claim 23.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 35-37 are rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner has rejected the claims for lack of enablement based on four allegations:

1) There is no disclosure of a correlation between any specific disease state and endothelin receptor activity.
2) There are no working examples of diseases resulting from abnormal endothelin receptor activity or compounds other than endothelin which bind to the endothelin receptor of SEQ ID NO: 1.
3) One skilled in the art would doubt that the claimed method would work due to unknowns.
4) There is no connection (nexus) between the compound in the claims and the disease state in the claims.

Regarding 1), the utility of the invention should not be considered to be relegated to the treatment of a specific disease state. Rather, the utility is the treatment of *any* disease that is discovered to be characterized by abnormal endothelin receptor activity. Since the endothelin receptor of SEQ ID: 1 is novel, no related diseases had been characterized as of the filing date of the present application. However, the claimed subject matter provides a tool for treating any disease that may be characterized after the filing date to have abnormal endothelin receptor activity. It is not necessary for those skilled in the art to evaluate all possible endothelin receptor-related conditions. Rather it is only necessary to those skilled in the art to apply the present invention to any given endothelin receptor-related condition.

Regarding 2), even though there are no working examples of diseases related to abnormal endothelin receptor activity or other compounds which bind to the endothelin receptor, one skilled in the art would have found it evident from the specification as filed that diseases related to abnormal endothelin receptor activity exist, and that it would be possible to routinely screen for compounds which agonize/antagonize endothelin receptor activity.

Regarding 3), because the compound is detected to bind to the endothelin receptor and affect its activity, the unknowns listed by the Examiner would not apply to a disorder

characterized by abnormal endothelin receptor activity. Since the compound affects the endothelin activity, it would be rationally expected to work on the disorder.

Regarding 4), the Examiner is fundamentally incorrect. The nexus between the compound and the disease state is the endothelin receptor itself. Further, the Examiner's assertion that the endothelin receptor may not be the "rate-limiting step" is misguided. Because the condition is characterized by abnormal endothelin receptor activity, then normalizing the endothelin receptor activity would be rationally expected to normalize the activity of biological pathways downstream from the receptor, and therefore normalize the condition.

Evidentiary Exhibits

Applicant submits herewith evidence that the endothelin receptor of the present invention can be successfully used as a screening target and that a drug which binds to the endothelin receptor can have a useful pharmacological effect on conditions that are related to abnormal endothelin receptor activity. In particular, Exhibits Al through A10 are scientific articles demonstrating that recombinant endothelin receptors of the present invention (recombinant ET_A receptors) have been successfully used to screen and identify compounds which bind to the receptors and have useful pharmacological effect against ET_A-related conditions.

- Exhibit Al (Clozel et al, (1995) J. Pharm. Exp. Ther 270(1):228-234) describes that bosentan (RO 47-0203) was screened on recombinant and naturally occurring ET_A receptors and was subsequently shown to have in vitro and in vivo activity. See in particular the Abstract, "Binding Assays on Attached cells", "Binding Assays on Membranes", "Saturation binding", and Table 1.
- Exhibit A2 (Murugesan et al, (2000) J. Med. Chem 43:3111-3117) describes that a class of ET_A receptor antagonists were screened using recombinant ET_A-expressing cells, and that an optimal candidate BMS-193884 was shown to lower mean arterial pressure in DOCA salt hypertensive rats. See in particular the Abstract, "Radioligand Binding Assays", Table 1 and Figure 2.

- Exhibit A3 (Yamauchi et al (1997) Jap. J. Pharm. 73(Sup I) 0-133), and Exhibit A4 (Murata et al (1997) Jap. J. Pharm. 73(Sup I) S9-2) describe that the endothelin receptor antagonist T-0201 was screened with cloned ET_A receptors and was also shown to inhibit the pressor response in vivo in rats and dogs.
- Exhibit A5 (Nakao et al (2000) Jap. J. Pharm 82 (Sup I) 0-148) describes the ET_A antagonist J-104132 also decreased blood pressure in several types of hypertensive rats.
- Exhibit A6 (Liu et al (1998) J. Mad Chem. 41:3261-3275) describes screening of a class of pyrrolidine-3-carboxylic acids against the ET_A receptor and the identification of a highly selective ET_A antagonist A-216546 as well as several other backup compounds. See in particular Abstract and Tables 1-5.
- Exhibit A7 (Roux et al (1997) J. Pharm. Exp. Ther 283(3):110-1118) describes compound Ro 61-1790 which was screened to have sub-nanomolar affinity for recombinant ET_A receptors, and shown to have in vivo effectiveness against subarachnoid hemorrhage. See in particular Abstract, "Binding Assay", Table 1 and Figure 5.
- Exhibit A8 (Repine et al (1998) Abstracts of the 216th ACS National Meeting 019) report screening of endothelin antagonists on cloned ET_A receptors to isolate the potent antagonist PD180988, which was also disclosed to have strong functional activity.
- Exhibit A9 (Clozel et al (1999) J. Pharm. Exp. Ther. 290(2) 840-846) reports the new endothelin receptor antagonist tezosentan which was screened on ET_A-expressing cells, and shown to decrease blood pressure in vivo. See in particular Abstract, "Binding Assays on Membranes", "Binding Assays on Attached Cells", table 1, and Figures 3 and 5.

- Exhibit A10 (Amberg et al (1999) J. Med. Chem 42:3026-3032) reports synthesis and screening of a family of endothelin-A antagonists, and the selection of LU 302872 as the most active derivative which has in vivo efficacy against blood pressure.

In addition to Exhibits A1 through A10, we also provide Exhibit B (both in Japanese and an English translation). Exhibit B is a data sheet regarding the clinical development of Bosentan. As shown in Exhibit Al, the endothelin receptor antagonist Bosentan was identified as a result of screening against the endothelin receptor A (the receptor of the present invention). Exhibit B describes in detail that Bosentan has been indicated for conditions including heart failure and pulmonary hypertension and is likely to be released onto the market in the near future. It is noted that these are among the conditions admitted by the Examiner to be known to be related to endothelin and endothelin receptors.

CONCLUSION

Applicant has, by way of the amendments and remarks presented herein, made a sincere effort to overcome rejects and address all issues that were raised in the outstanding Office Action. Accordingly, reconsideration and allowance of the pending claims are respectfully requested. If it is determined that a telephone conversation would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant(s) petition(s) for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 299002032411.

Respectfully submitted,

Dated: April 10, 2003 By: _____

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